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# Markers for creatinine height after percutaneous coronary intervention in patients with normal renal function



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**Abstract**

Aim: We aimed to research the risk indicators of high-level creatinine in patients with normal renal functions, following percutaneous coronary intervention (PCI).

Material and Methods: Two hundred thirty-eight patients who were subjected to PCI were enrolled in our study. The present single-centered observation study was carried out retrospectively. Pre-intervention serum creatinine values were below 1,2 mg/dl, and information about patients who underwent percutaneous coronary intervention (PCI) was obtained. The patients included in the study were divided into two groups according to creatinine values at 24 hours after intervention (Group 1: patients with creatinine (CRE) <1,2 mg/dl after PCI; Group 2: patients with CRE≥1,2 mg/dl after PCI). These two groups were also examined separately according to risk factors. The patients were given 100-300 ml low osmolar nonionic monomer iopromide (Ultravist vial, 370-200 ml vial) during intravenous PCI.

Results: The size of Group 1 was 18,5% (n = 44) and the size of Group 2 was 81,5% (n = 194). When these groups were compared in terms of risk factors, heart failure (25% n=11) and male gender (77,3%, n=34) were found to be independent risk factors in the development of contrast media nephropathy (p<0,035 and p<0,006, respectively). In addition, in the correlation analysis, it was found that the patients whose CRE levels were very high in their follow-ups also increased significantly in the same correlation in the same degree of heart failure.

Discussion: Contrast-induced nephropathy (CIN) should consider the risk factors in all interventions using contrast media, and special care should be exercised in high-risk patients with male gender and/or heart failure.

**Keywords**

Percutaneous coronary intervention (PCI); Heart failure; Contrast-induced nephropathy (CIN)

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## Introduction

Contrast-induced nephropathy (CIN) is an often reversible form of acute renal failure (ABY) that occurs after intravascular radiocontrast administration [1]. Contrast media-associated ABY has been increasing in recent years in both inpatient and outpatient patients [2]. Even a small increase in creatinine level in patients with CIN has been associated with an increase in morbidity and mortality [3]. In patients using CIN intravascular radiographic contrast media, it is defined as the development of acute renal failure (ABY) within 48 hours after the procedure, regardless of the need for any clinical symptoms or hemodialysis [4, 5]. For patients without any risk factors, the risk of CIN is low even after intraarterial injection and is around 2% [3, 6]. Angiography and percutaneous coronary intervention are the most important causes leading to CIN and the risk of CMN after these procedures; while it is around 2% in patients with normal kidney function, it is up to 20-30% in patients with basal creatinine level above 2 mg/dl [7, 8]. It has been shown that 13% of all ABY cases are secondary to the use of contrast media, while the third most common cause of ABY occurring within the hospital is CIN [9]. A different definition of CIN is 25% or 44 μmol / L (0.5mg / dl) increase in serum creatinine level within three days after the administration of contrast media, without any other etiological reason [10, 11]. Development of CIN is clinically associated with long- and short-term survival, and hemodialysis needs are linked to increased hospitalization, increased cost, increased mortality and morbidity [12, 13].

Various risk factors have been identified for the development of CIN. Age, hypertension (HT), diabetes (DM), pre-existing kidney failure, type and amount of contrast media, place of administration (IV, IA) and frequency of administration, New York Heart Association (NYHA) Stage III-IV congestive heart failure and left low ventricular ejection fraction, decreased intravascular volume, dehydration, cardiogenic shock and hypotension are defined as risk factors [14].

The increased use of contrast media in diagnostic and interventional cardiac catheterization procedures has made contrast media nephropathy a common problem in clinical cardiology practice. This important clinical problem, which may be associated with high mortality and morbidity, is still not adequately identified by physicians. Chronic kidney failure is the main predisposing factor for CIN [15]. The exact mechanism of CIN is not known in detail. It is accepted that alteration of kidney hemodynamics and direct tubular toxic effect of contrast media are the main cause of CIN [15].

Various studies have been carried out to prevent CIN, and the accepted application is hydration (increasing extracellular volume), and the type and amount of contrast media are adjusted [16, 17].

The aim of this study was to determine the possible risk factors of CIN that may develop after percutaneous coronary intervention in adults with normal renal function and coronary artery disease, and to investigate the correlation between these risk factors and CIN.

## Material and Methods

### *Patients*

The research study was approved by the Yeditepe University Health Sciences Ethics Committee. Written informed consent was obtained from all participants of the study. For this study, 238 patients with normal renal function who underwent PCI between 2009 and 2010 at the Cardiology Clinic of Yeditepe University Medical School were included in the study. Patients with known chronic renal failure, pre-procedure creatinine (CRE) value above 1,2 mg/dl and known to be allergic to contrast media were excluded from the study.

### *Study Design*

This single-center observation study was carried out retrospectively. Before the procedure, serum creatinine values were below 1,2 mg/dl and percutaneous coronary intervention was performed, and the information of the patients who met the inclusion criteria was obtained. Patients' age, gender, concomitant diseases, the nephrotoxic drugs they used and the history of contrast media use in the last month were recorded. Before the intervention, serum sodium (NA), potassium (K), blood urea nitrogen (BUN), creatinine (CRE) and complete blood count measurements were made. Blood pressure of the patients measured manually was recorded before the procedure. In addition, the left ventricular ejection fraction (EF) values were recorded from echocardiographs performed within 1 week before the intervention. Heart failure was defined as EF <50%. BUN and CRE levels of all patients were examined for the first 24 hours after the intervention. In cases with increased CRE levels, 48th and 72nd hour BUN and CRE levels were examined. The patients included in the study were divided into two groups according to CRE values at 24 hours after the procedure (Group 1: patients with CRE <1,2 mg/dl after PCI; Group 2: patients with CRE≥1,2 mg/dl after PCI). These two groups were also examined separately according to risk factors.

### *Hydration protocol*

A total of 500ml 0.9% NACL liquid (100-120 ml / h) was administered to all patients via a peripheral intravenous (IV) before PCI. All patients were taken to PCI procedure between the second and third hours after starting the infusion. After the intervention, a total of 1000ml 0.9% NACL liquid (100-120 ml / hour) was administered via a peripheral intravenous (IV) route. In contrast, patients with EF below 50% received intravenous (IV) intravenous (IV) fluid after the procedure at 100-120 ml/ hour. All patients were given 100-300ml low osmolar nonionic monomer iopromide (Ultravist vial, 370-200ml vial) during intravenous percutaneous coronary intervention (PCI).

### *Statistical analysis*

SPSS 13 computer program was used for statistical analysis of the study. Quantitative data were defined as X + SD (mean ± standard deviation). One-way ANOVA significance test was performed to compare the analyzed data between the groups by normality. The Scheffe procedure was used to determine which group was different. The comparison between basal values and other times was made using the Repeated Variance Analysis materiality test. The Bonferroni test was used to determine which time was different. The distribution in qualitative data was expressed as a percentage. The chi-square ($x^2$) test was used to determine statistical significance between the appropriate data. The comparison of contrast media nephropathy between the two groups was made using the Hosmer Lemoshow test. Regression analysis Wald test was used

to determine dependent and independent risk factors (markers) causing contrast substance nephropathy. Pearson Correlation Coefficient was calculated to determine the relationship between two quantitative variables. The significance level was accepted as <0,05.

## Results

Records of 238 patients with normal renal function that met the inclusion criteria were examined. The ages of the cases ranged between 32 and 90 years, with an average of 63,2 ± 17,9 years; 36,5% of the patients (87) were women; 63,45% (151) of them were male cases. According to the CRE value after PCI, 194 patients were included in Group 1 and 44 patients were included in Group 2. Group 1 and Group 2 were compared in Table 1 in terms of demographic characteristics and possible CIN risk factors. Group 1 included 117 males (60,3%) and 77 females (39,7%), Group 2 included 34 males (77,3%) and 10 females (22,7%). There was a statistically significant difference between the gender distributions of the groups (p<0,05). Group 1 included 49 patients (25,3%) over 70 years old and 145 patients (74,7%) under 70 years old, Group 2 included 15 patients (34,1%) over 70 years old and , 29 patients under 70 years old (65,9%). There was no statistically significant difference in the age distribution between the groups (p>0,05). The number of diabetic patients in Group 1 was 67 (34,5%) and the number of diabetic patients in Group 2 was 12 (27,3%). There were 141 patients (72,7%) in Group 1 and 34 patients (77,3%) in Group 2. Coronary artery disease (CAD) was observed in 115 patients (59,3%) in Group 1and 28 patients (63,6%) in Group 2. The number of Atrial fibrillation (AF) was 12 (6,2%) in Group 1 and 5 (11,4%) in Group 2. There was no statistically significant difference between the groups in terms of diabetes, hypertension, CAD and AF distributions (p>0,05). The frequency of heart failure (HF) was evaluated in two groups. In Group 1, 19 patients (9,8%) and in Group 2, 11 patients (36,7%) had HF. There was a statistically significant difference in the distribution of HF in these patients (p<0,05). Also, the correlation with CRE was investigated in patients whose EF was below 50% and CIN developed. In the correlation analysis, it was found that the size of the CRE height that occurred during the follow-ups showed a significant negative relationship with the degree of HF (shown as the EF value) (r=-0,255, p<0,05) (Figure 1). This analysis was tested with the Hosmer-Lemeshow test and it was determined that the regression equation is a suitable model (p>0,05). Contrast media use history was examined in the last 1 month in both groups. Thirty-seven patients (19,2%) in Group 1 and 5 patients (11,4%) in Group 2 had a history of contrast media (CM) use within the past month. No statistically significant difference was found between the distributions of these patients according to their history of using CM (p>0,05). The potassium and sodium values of the patients examined before the procedure were within normal values.

Independent variables in CIN are shown in Table 2. In our study, male gender and HF were found as independent variables for CRE height to develop after PCI. For the male gender, variables were as follows: p=0,038, OR: 2,27 and 95% CI: 1,048 – 4,932. Accordingly, the risk of CRE≥1.2 mg / dl after PCI increased 2,27 times compared to women. For heart failure (HF), p=0,008, OR: 3,151 and 95% CI: 1,354 – 7,336. Accordingly, in those with HF, the risk of CRE≥1,2 mg/dl after PCI increased by 3,151 times compared to those without HF (Table 2).

**Table 1.** Demographic features of the study group

| | Group 1 (n=194) Cre<1,2 | Group 2 (n=44) Cre>=1,2 | P-value* |
|---|---|---|---|
| Gender | | | |
| Female | | 10 (22,7%) | 0,035* |
| Male | 117(60,3%) | 34 (77,3%) | |
| Age group | | | |
| <55 age | 59 (30,4%) | 8 (18,2%) | |
| 55-70 age | 86 (44,3%) | 21 (47,7%) | 0,219 |
| >70 age | 49 (25,3%) | 15 (34,1%) | |
| DM | | | |
| No | 127 (65,5%) | 32 (72,7%) | 0,356 |
| Yes | 67 (34,5%) | 12 (27,3%) | |
| HT | | | |
| No | 53 (27,3%) | 10 (22,7%) | 0,533 |
| Yes | 141 (72,7%) | 34 (77,3%) | |
| CAD | | | |
| No | 79 (40,7%) | 16 (36,4%) | 0,594 |
| Yes | 115 (59,3%) | 28 (63,6%) | |
| EF | | | |
| >=50% | 175 (90,2%) | 33 (75,0%) | 0,006* |
| <50% | 19 (9,8%) | 11 (25,0%) | |
| AF | | | |
| No | 182 (93,8%) | 39 (88,6%) | 0,229 |
| Yes | 12 (6,2%) | 5 (11,4%) | |
| Nephrotoxic drug | | | |
| No | 192 (99,0%) | 44 (100%) | 1,000 |
| Yes | 2 (1,0%) | 0 (0%) | |
| Repetitive process | | | |
| No | 156 (%80,8) | 39 (88,6%) | 0,221 |
| Yes | 37 (%19,2) | 5 (11,4%) | |
| Na | 138,2±3,8 | 138,8±3,5 | 0,222 |
| K | 4,123 | 4,128 | 0,364 |

Na: Sodium, K: Potassium, DM: Diyabetes mellitus, HT: Hypertension, AF: Atrial fibrillation, EF: Ejection fraction, CAD: Coronary artery disease.

**Table 2.** Independent variables for contrast induced nephropathy (CIN)

| | B | S.E | Wald | P value | OR | 95% CI Min - Max |
|---|---|---|---|---|---|---|
| Gender | 0,821 | 0,395 | 4,318 | 0,038 | 2,273 | 1,048 - 4,932 |
| HF | 1,148 | 0,431 | 7,091 | 0,008 | 3,151 | 1,354 -7,336 |
| Constant | -2,238 | 0,356 | 39,436 | 0,000 | 0,107 | |

HF: Heart failure, OR: Odds ratio.

## Discussion

CIN is a frequently encountered problem in clinical practice. With the increase in the use of contrast media in diagnoses and interventions over the past three decades, CIN has become the third common cause of ESI acquired in the hospital [1]. The development of CIN depends on the physical and chemical properties of the media used, along with the patient's existing characteristics.

The negative effect of contrast-mediated nephropathy on

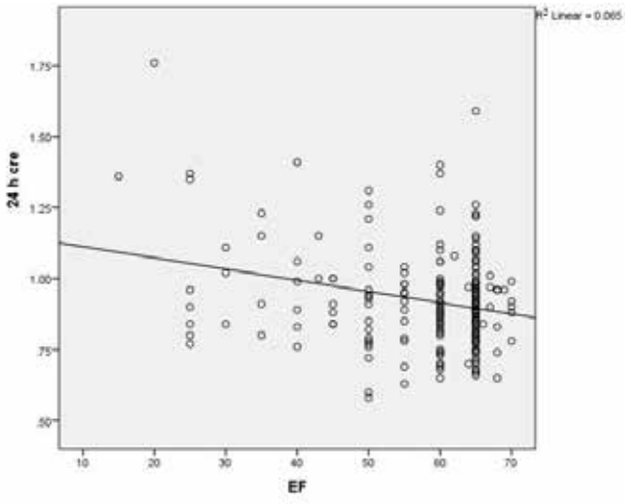


**Figure 1.** Correlation analysis between Creatinine (CRE) height and heart failure (HF) grade (shown as the ejection fraction (EF) value)

the clinical results of patients undergoing diagnostic and interventional procedures is well known [1, 6, 8, 15]. Today, there is no cure to reverse or correct contrast media nephropathy once it occurs, but prophylaxis is possible. However, most of these methods were found to be useless in well-designed, prospective, randomized double-blind studies [10]. This group of treatments includes diuretics, mannitol, dopamine, atrial natriuretic peptide, endothelin receptor antagonists and phenoldopam [18, 19].

Hydration is the primary intervention in the prevention of contrast nephropathy [20]. The mechanism of hydration reduces the activity of the renin-angiotensin system, decreases the levels of other vasoconstrictor hormones such as endothelin, increases sodium diuresis, decreases the tubuloglomerular feedback cycle, prevents tubular obstruction, protects against reactive oxygen species and ensures that the contrast media is diluted at the tubular level, is to reduce any direct nephrotoxic effect [21]. Hydration with saline infusion is useful for preventing contrast-induced nephropathy. Intravenous hydration has become a standard method for the prevention of contrast-induced nephropathy [22].

Our study was planned primarily to evaluate the markers of patients with normal renal function in our clinic that may cause contrast media nephropathy after PCI. In our study, it was found that heart failure and male gender are independent risk factors for the development of contrast media nephropathy in patients with normal renal function. There are different data in the literature regarding male gender and CIN risk. Mehran et al. have shown that gender has a strong relationship with other CIN risk factors and men are 3.2 times at the risk of CIN than females [23]. Similarly, in our study, male gender was found statistically significant in terms of CIN development. However, another study on 8628 people showed that women are more risky in terms of CIN development [24]. The general approach is that men are at higher risk.

In patients with heart failure, especially if the EF value is below 50%, the patients' cardiac performance is impaired and their renal perfusion also deteriorates, and when these patients are exposed to radiocontrast, CIN development rates are higher than in normal individuals [25]. Similarly, in our study, the risk of developing contrast media nephropathy was significantly increased in patients with HF ($p<0,05$). There are studies in the literature supporting the findings of our study. In a study, if the EF value of patients undergoing coronary angiography is not below 30%, it was shown that the EF values of these patients did not have a significant effect on the development of contrast media nephropathy [25]. In addition to these findings, we found a significant negative correlation between EF and post-PCI CRE values in our study. This shows that as the EF value decreases, CRE values after PCI increase.

*Limitations*

Although it was not statistically significant in terms of other risk factors in our study, in some studies, history of coronary artery disease in the last month, age, diabetes mellitus and history of contrast agent use were shown as risk factors for CIN. In our study, due to the low number of patients developing CIN, these parameters may not have reached statistical significance, which will be risk factors.

*Conclusion*

CIN is an important, preventable and reversible condition due to hospital cost and its effects on patient morbidity and mortality. Today, there is a resistance to the prevention of contrast media nephropathy. There are two reasons for this: the first is that a good preventive intervention cannot be done before the procedure, and the second is that the physicians performing the intervention cannot predict the risk of patients before the procedure. Awareness should be at the forefront in order to prevent CIN development. Therefore, CIN should consider the risk factors in all interventions using contrast media. Particular attention should be paid to pre-hydration, appropriate pharmacological support, the use of contrast substances with low toxic potential, and the absence of concomitant nephrotoxic medias, when high-risk patients such as male gender and heart failure are required to be given contrast media.

***Scientific Responsibility Statement***

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

***Animal and human rights statement***

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.*

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***Conflict of interest***

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